REMARKS

Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are pending in the application and have been rejected. Claims 4, 8, 36, 38, 39, 41, and 42 have been amended. Reconsideration and allowance of Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 in view of the above amendment and following remarks is respectfully requested.

The Rejection of Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-46 Under 35 U.S.C. § 112, Second Paragraph.

Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-46 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner is of the opinion that the use of the term "vinyl-type" is indefinite.

Claims 36, 38, 39, 41, and 42 have been amended to remove the term "vinyl-type." Applicants submit that amended Claims 36, 38, 39, 41, and 42, and dependent Claims 3, 4, 8, 9, 13-17, 19, 34-35, 40, and 43-45 are definite. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 Under 35 U.S.C. §§ 102(b)/103(a).

Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Davaran et al. (Davaran et al., "Hydrophilic Copolymers Prepared From Acrylic Type Derivatives of Ibuprofen Containing Hydrolyzable Thioester Bond", *European Polymer Journal 34*(2):187-192, 1998) and Baroni et al. (Baroni et al., "Effect of Ibuprofen and Warfarin on the Allosteric Properties of Haem-Human Serum Albumin," *European Journal of Biochemistry 268*:6214-6220, 2001). Withdrawal of the rejection is requested for the following reasons.

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Claims 36, 38, 41, and 47 are the pending independent claims. Claims 3, 4, 8, 9, 13-15, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

The claimed invention relates to a water-soluble hydrophilic conjugate that includes two components, a hydrophilic component and a hydrophobic component, that are linked by a pH-sensitive linkage. The pH-sensitive linkage is stable at a pH between 6.8 and 8 and is hydrolyzed at a pH less than 6.5. The hydrophobic component is a vinyl polymer that is membrane disruptive when released from the conjugate by hydrolysis of the pH-sensitive linkage. The hydrophilic component includes a polyalkylene oxide.

Each of the elements noted above are recited in each of independent Claims 36, 38, 41, and 47. Claim 47 further recites that the hydrophobic component is a random, block, or graft copolymer. The cited references fail to teach or suggest a composition that includes each and every element of the claimed invention. The cited references fail to teach or suggest a composition that releases a hydrophobic vinyl polymer that is membrane disruptive on hydrolysis of a pH-sensitive linkage.

The Davaran reference describes hydrophilic copolymers of ibuprofen. The copolymers are prepared by copolymerization of a drug containing monomer (S-methacryloyloxyethyl-α-methyl-4-(2-methylpropyl)benzenethioacetate (MOETE)) and a comonomer (i.e., methacrylic acid, methacrylamide, vinyl imidazole, and polyethylene glycol methacrylate). See page 188 first full paragraph and Scheme 2 at page 189. Release of ibuprofen from the copolymers is illustrated in Figures 1-3 at page 190. Ibuprofen is released from the copolymer by hydrolysis of the thioester bond intermediate the ibuprofen moiety and the oxyethylene spacer arm on the MOETE moiety. See Abstract and Scheme 2 at page 189.

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As an initial matter, applicants note that the reference describes release of ibuprofen from the copolymer at pH 8.5 at 37°C and measurable release only occurs after an extended period (i.e., about 30% release after 40 hours, Figure 1; about 50% release after 40 hours; Figure 2; and about 80% release after 50 hours, Figure 3). Applicants note that the claimed compositions have a pH-sensitive linkage intermediate the hydrophobic component and hydrophilic component that is stable at a pH between 6.8 and 8 (biological pH) and is hydrolyzed at pH less than 6.5 to release the hydrophobic component from the hydrophilic component. The claimed composition differs from the copolymers of the reference in that they are stable at the pH that the reference's copolymers are hydrolyzed. Moreover, applicants submit that the reference's copolymers are not hydrolyzable at a pH less than 6.5 to release ibuprofen.

Applicants further call the Examiner's attention to Claim 15, which depends from Claim 36 and recites that the pH sensitive linkage is hydrolyzed within about 30 to 60 minutes at a pH between 5.0 and 5.5.

In contrast to the claimed invention, the cited reference fails to teach or suggest a composition having a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage that, on hydrolysis, delivers a hydrophobic polymer that is membrane disruptive. The Davaran reference describes a copolymer having a hydrolyzable thioester group that is capable of releasing a hydrophobic drug, ibuprofen. On hydrolysis of the thioester, ibuprofen is released from the copolymer leaving behind the copolymer less its previously covalently coupled drug moiety. Hydrolysis of the thioester bond releasing ibuprofen does not provide a hydrophobic polymer that is membrane disruptive. Even assuming that the copolymer of the reference includes a hydrophobic component (vinyl polymer) and a hydrophilic component (polyalkylene oxide), release of ibuprofen does not provide release of the hydrophobic component as defined in the claimed invention.

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The claimed invention relate to a conjugate that includes a hydrophobic component (vinyl polymer) that, on hydrolysis of the pH-sensitive linkage (stable at pH 6.8 to 8 and hydrolytic at pH less than 6.5) that covalently couples the hydrophobic component to the hydrophilic component (polyalkylene oxide), releases a vinyl polymer that is membrane disruptive.

Regarding the MOETE-PEGM copolymer described in the Davaran reference, hydrolysis of the ester linkage intermediate the PEG group and the poly(methylacrylate) backbone does not provide a hydrophobic component (i.e., vinyl polymer) that is membrane disruptive. Hydrolysis yields a poly(methylacrylic acid) that is not membrane disruptive. Enclosed herewith as **Exhibit A** is the Declaration of Patrick Stayton evidencing the differences in behavior for several poly(alkylacrylic acids): poly(methylacrylic acid), poly(ethylacrylic acid), and poly(propylacrylic acid). Unlike higher alkyl poly(alkylacrylic acids), poly(methylacrylic acid) is insufficiently hydrophobic to be membrane disruptive. While poly(ethylacrylic acid) and poly(propylacrylic acid) are effective in membrane disruption, poly(methacrylic acid) is not.

Finally, applicants submit that the independent claims' recitation that the hydrophobic component is membrane disruptive is not an intended use, but rather an element of the claim that must be afforded patentable weight.

Because the Davaran reference fails to describe a copolymer that releases a hydrophobic vinyl polymer that is membrane disruptive on hydrolysis of a pH-sensitive linkage, the reference fails to exactly disclose the claimed invention and therefore is not anticipatory. Withdrawal of the Section 102 rejection is requested.

Applicants further submit that the cited reference fails to teach or suggest the claimed invention. The cited reference fails to teach or suggest the use of any polymer or copolymer other than the disclosed methacrylates. Nor does the reference suggest or provide any apparent

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reason why one of skill would substitute a higher alkyl poly(alkylacrylic acid) for the poly(methacrylic acids) described in the reference.

The Davaran reference discloses polymeric-drug conjugates for delivering ibuprofen to solve the drug's irritant side effects on the gastro-enteric mucosa and its poor water solubility. Hydrophilic comonomers, such as methacrylic acid, methacrylamide, vinyl imidazole, and polyethylene glycol methacrylate, were used to copolymerize with MOETE to solubilize the drug. According to Davaran, the copolymers obtained showed water solubility sufficient for homogeneous hydrolysis of the polymeric-drug conjugates disclosed in the reference (page 190, right column). Applicants further submit that it is well known to the skilled person to use polyethylene glycol methacrylate (PEGM) as a solubilizer for hydrophobic drugs or polymers. See, for example, page 190, right column; and Akashi, M., "Polymer for Pharmaceutical and Biomolecular Engineering in Biomedical Applicants of Polymeric Materials," T. Tsuruta (ed.), CRS Press Inc., Boca Raton, Florida, 1993. Because the problem associated with the solubility of the polymeric prodrug has been satisfactorily solved by using the disclosed hydrophilic comonomers and further because polyethylene glycol methacrylate (PEGM) is well-known in the field of art as a solution for solubilizing hydrophobic drugs or polymers, there are no apparent reason to further modified Davaran's teaching to arrive at the claimed invention.

For the reasons set forth above, because the cited references fail to teach, suggest, or provide any motivation to make the claimed invention and because there is no apparent reason to modify the cited references according to the claimed invention, the claimed invention is not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

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The Rejection of Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 Under 35 U.S.C. § 103(a).

Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable over the combined teachings of the Davaran reference, the Baroni reference, Vinogradov et al. (Vinogradov et al., "Self-Assembly of Polyamine-Poly(ethylene glycol) Copolymers with Phosphorthioate Oligonucleotides," *Bioconjugate Chemistry* 9:805-812, 1998), and U.S. Patent No. 4,571,400, issued to Arnold. Withdrawal of the rejection is requested for the following reasons.

Claims 3, 4, 8, 9, 13-17, 19, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

The deficiencies of the teachings of the Davaran and Baroni references noted above with regard to independent Claims 36, 38, 41, and 47 are not cured by the teachings of the Vinogradov and Arnold references.

The Vinogradov reference teaches cationic copolymer for DNA delivery by conjugating poly(ethylene glycol) (PEG) and polyamines: polyspermine (PSP) and polyethylenimine (PEI). The cationic copolymers comprise the conjugates of polyethylene glycol (PEG) and polyamines. The PEG and the polyamines are linked through a carbamate linker, i.e., -NH-COO-. The cationic copolymers are complexed to antisense oligonucleotides (PS-ODNS).

The Arnold reference is directed to pharmaceutical compositions containing dihydrocodeine or a pharmaceutically acceptable acid addition salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof that are useful in treating pain. The reference discloses a wide range of pharmaceutically acceptable carriers for use with ibuprofen.

Because the cited references, either alone or in any combination, fail to teach, suggest, provide any motivation, or otherwise render obvious the claimed invention, the claimed

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invention is not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of above amendments and foregoing remarks, applicants believe that Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are in condition for allowance. If any issue remains that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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